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FILE 'CAPLUS' ENTERED AT 09:43:39 ON 20 APR 2006
            E CHENG JINAJUN/IN,AU
            E CHENG JIANJUN/IN,AU
L1           43 S E3-4
            E DAVIS MARK/IN,AU
L2          410 S E3-4 OR E15-18
            E KHIN KAY/IN,AU
L3           12 S E4-6
L4          447 S L1 OR L2 OR L3
L5        30739 S CYCLODEXTRIN
L6      1922726 S POLYMER?
L7           38 S L4 AND L5 AND L6
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L7 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:248377 CAPLUS
TITLE: Engineered **polymers** for targeted delivery of siRNA
AUTHOR(S): Heidel, Jeremy D.; **Davis, Mark E.**
CORPORATE SOURCE: Colando Pharmaceuticals, Duarte, CA, 91010, USA
SOURCE: Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006 (2006), MEDI-225. American Chemical Society: Washington, D. C.
CODEN: 69HYEC
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB RNA interference (RNAi) is becoming the method of choice for target validation studies that involve gene inhibition. While localized delivery of siRNA is now used in early clin. trials (direct injection into the eye), many diseases will require systemically delivered therapies, e.g., metastatic cancer. Numerous issues must be addressed when considering the systemic delivery of siRNA as a generalized gene inhibition strategy against human disease. In order to have repeatable, systemic dosing of siRNA that provides a cost effective therapy, we believe that non-viral delivery systems must be employed. We will show that a **cyclodextrin**-based **polymeric** delivery system can provide systemic delivery of non-chemical functionalized siRNA at doses and via routes of administration that are applicable to human therapy. EDs in animals are at least an order of magnitude below those used with chemical modified siRNAs lacking delivery systems, and this feature provides for a more cost-acceptable therapeutic. The delivery system contains a targeting ligand to enhance delivery to the desired tissue and an optimized siRNA sequence to provide potent and long-lasting gene inhibition. The delivery system protects unmodified siRNA from degradation in serum and does not produce an immune response. Results illustrating all of these essential features of the therapeutic will be presented.

L7 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:205526 CAPLUS
TITLE: Preclinical Efficacy of the Camptothecin-**Polymer** Conjugate IT-101 in Multiple Cancer Models
AUTHOR(S): Schluep, Thomas; Hwang, Jungyeong; **Cheng, Jianjun**; Heidel, Jeremy D.; Bartlett, Derek W.; Hollister, Beth; **Davis, Mark E.**
CORPORATE SOURCE: Authors' Affiliations: Insert Therapeutics
SOURCE: Clinical Cancer Research (2006), 12(5), 1606-1614
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Preclin. efficacy of i.v. IT-101, a nanoparticulate conjugate of 20(S)-camptothecin and a **cyclodextrin**-based **polymer**, was investigated in several mouse xenografts. The effects of different multiple dosing schedules on tumor growth of LS174T colon carcinoma xenografts are elucidated. All multiple dosing schedules administered over 15 to 19 days resulted in enhanced efficacy compared with untreated or single-dose groups. Further improvements in antitumor efficacy were not observed when the dosing frequency was increased from three weekly doses to five doses at 4-day intervals or 5 days of daily dosing followed by 2 days without dosing repeated in three cycles using similar cumulative doses. This observation was attributed to the extended release characteristics of camptothecin from the **polymer**. Antitumor efficacy was further evaluated in mice bearing six different s.c. xenografts (LS174T and HT29 colorectal cancer, H1299 non-small-cell lung cancer, H69 small-cell lung cancer, Panc-1 pancreatic cancer, and MDA-MB-231 breast cancer) and one disseminated xenograft (TC71-luc Ewing's sarcoma). In all cases, a single treatment cycle of three weekly doses of IT-101 resulted in a significant antitumor effect. Complete tumor regression was observed in all animals bearing H1299 tumors and in the majority of animals with disseminated Ewing's sarcoma tumors. Importantly, IT-101 is effective in a number of tumors that are resistant to treatment with irinotecan (MDA-MB-231, Panc-1, and HT29), consistent with the hypothesis that **polymeric** drug conjugates may be able to overcome certain kinds of multidrug resistance. Taken together, these results indicate that IT-101 has good tolerability and antitumor activity against a wide range of tumors.

L7 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:142861 CAPLUS
TITLE: Pharmacokinetics and biodistribution of the camptothecin-**polymer** conjugate IT-101 in rats and tumor-bearing mice
AUTHOR(S): Schluep, Thomas; **Cheng, Jianjun; Khin, Kay T.; Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc., 3525 Nina Street, Pasadena, CA, 91107, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2006), 57(5), 654-662
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: IT-101 is a camptothecin-**polymer** conjugate prepared by linking camptothecin (CPT) to a hydrophilic, **cyclodextrin**-based, linear **polymer** through ester bonds. In previous studies, these **polymer** conjugates with high mol. wts. (ca 90 kDa) have shown significant antitumor effects against human colon carcinoma xenografts. The pharmacokinetics of IT-101 in plasma of rats and its biodistribution in nude mice bearing human LS174T colon carcinoma tumors is reported here. Methods: Sprague-Dawley rats were injected i.v. with three different doses of IT-101. Serial plasma samples were analyzed for **polymer** -bound and unconjugated CPT by high-performance liquid chromatog. (HPLC). Concentration vs time data were modeled using non-compartmentalized methods and compared to CPT alone injected i.v. at an equivalent dose. Tumor-bearing mice were injected i.v. with IT-101 and i.p. with CPT alone, and sacrificed after 24 and 48 h, and serum, heart, liver, spleen, lungs and tumor collected. Tissue samples were extracted and analyzed for **polymer** -bound and unconjugated CPT by HPLC. Results: Plasma concns. and the area under the curve for **polymer**-bound CPT are approx. 100-fold higher than those of unconjugated CPT or CPT alone, injected i.v. at an equivalent dose. The plasma half-life of IT-101 ranges from 17 -20 h and is significantly greater than that of CPT alone (1.3 h). When CPT is conjugated to **polymer**, the biodistribution pattern of CPT is different from that taken alone. At 24 h post injection, the total CPT per g of tissue is the highest in tumor tissue when compared to all other tissues tested. Tumor concns. of active CPT released from the conjugate are more than 160-fold higher when administered as a **polymer** conjugate rather than as CPT alone. Conclusions: The studies presented here indicate that i.v. administration of IT-101, a **cyclodextrin** based **polymer**-CPT conjugate, gives prolonged plasma half-life and enhanced distribution to tumor tissue when compared to CPT alone. The data also show that active CPT is released from the conjugate within the tumor for an extended period of time. These effects likely play a significant role in the enhanced antitumor activity of IT-101 when compared to CPT alone or irinotecan.

L7 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1311709 CAPLUS
DOCUMENT NUMBER: 144:40856
TITLE: Biodegradable drug-**polymer** delivery system containing ciprofloxacin β- **cyclodextrin** derivative inclusion complexes
INVENTOR(S): **Davis, Mark E.**; Wright, Kenneth W.; Mack, Brendan
PATENT ASSIGNEE(S): California Institute of Technology, USA
SOURCE: U.S. Pat. Appl. Publ., 44 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005276841	A1	20051215	US 2005-148011	20050607
WO 2005120578	A2	20051222	WO 2005-US19998	20050607

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-577906P P 20040607
US 2004-631448P P 20041129

AB A sustained-release biodegradable **polymeric** drug-eluting fiber is disclosed. In some embodiments, the therapeutic drug is complexed with **cyclodextrin**. The **polymeric** component of the fiber comprises **cyclodextrin**. The fiber may be fabricated to provide a thread and/or suture. The fiber may be used for treatment of ocular diseases or disorders. Solid inclusion complex of ciprofloxacin with hydroxypropyl, randomly methylated, and sulfobutyl ether β-**cyclodextrins** were prepared Drug eluting fibers were prepared from glycolic acid-lactic acid copolymer and the ciprofloxacin inclusion complexes were combined with the fibers.

L7 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:559559 CAPLUS
DOCUMENT NUMBER: 143:253713
TITLE: Single cell kinetics of intracellular, nonviral, nucleic acid delivery vehicle acidification and trafficking
AUTHOR(S): Kulkarni, Rajan P.; Mishra, Swaroop; Fraser, Scott E.; **Davis, Mark E.**
CORPORATE SOURCE: Option in Biochemistry and Molecular Biophysics, Division of Biology, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Bioconjugate Chemistry (2005), 16(4), 986-994
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mechanistic understanding of the intracellular trafficking of nonviral nucleic acid delivery vehicles remains elusive. A live, single cell-based assay is described here that is used to investigate and quantitate the spatiotemporal, intracellular pH microenvironment of **polymeric** -based nucleic acid delivery vehicles. Polycations such as polyethylenimine (PEI), poly-L-lysine (PLL), β- **cyclodextrin** -containing **polymers** lacking or possessing imidazole termini (CDP or CDP-imid), and **cyclodextrin**-grafted PEI (CD-PEI) are used to deliver an oligonucleotide containing a single fluorophore with two emission lines that can be employed to measure the pH. Delivery vehicles were also sterically stabilized by addition of poly(ethylene glycol) (PEG) and investigated. The intracellular trafficking data obtained via this new methodol. showed that vectors such as PEI and CDP-imid can buffer the endocytic vesicles while PLL and CDP do not. Addnl., the PEGylated vectors reveal the same buffering capacity as their unstabilized variants. Here, the live cell, spatiotemporal mapping of these behaviors is demonstrated and, when combined with cell uptake and luciferase expression data, shows that there is not a correlation between buffering capacity and gene expression.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:477467 CAPLUS
DOCUMENT NUMBER: 143:168947
TITLE: Quantitating intracellular transport of polyplexes by spatio-temporal image correlation spectroscopy
AUTHOR(S): Kulkarni, Rajan P.; Wu, David D.; **Davis, Mark E.**; Fraser, Scott E.
CORPORATE SOURCE: Option in Biochemistry and Molecular Biophysics, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2005), 102(21), 7523-7528
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Quant. understanding how nonviral gene delivery vectors (polyplexes) are transported inside cells is essential before they can be optimized for gene therapy and medical applications. In this study, we used spatio-temporal image correlation spectroscopy (ICS) to follow

polymer-nucleic acid particles (polyplexes) of various sizes and analyze their diffusive-like and flow behaviors intracellularly to elucidate the mechanisms responsible for their transport. ICS is a quant. imaging technique that allows the assessment of particle motion in complex systems, although it has not been widely used to date. We find that the internalized polyplexes are able to use microtubule motors for intracellular trafficking and exhibit different transport behaviors for short (<10 s) vs. long (≈60 s) correlation times. This motion can be explained by a memory effect of the microtubule motors. These results reveal that, although microtubule motor biases may be present for short periods of time, resulting in a net directional velocity, the overall long-term motion of the polyplexes is best described as a random walk-like process. These studies suggest that spatio-temporal ICS is a powerful technique for assessing the nature of intracellular motion and provides a quant. tool to compare the transport of different objects within a living cell.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:176884 CAPLUS
DOCUMENT NUMBER: 143:392713
TITLE: Targeted delivery of RNA-cleaving DNA enzyme (DNAzyme) to tumor tissue by transferrin-modified, **cyclodextrin**-based particles
AUTHOR(S): Pun, Suzie H.; Tack, Frederik; Bellocq, Nathalie C.; **Cheng, Jianjun**; Grubbs, Brendan H.; Jensen, Gregory S.; **Davis, Mark E.**; Brewster, Marcus; Janicot, Michel; Janssens, Boudewijn; Floren, Wim; Bakker, Annette
CORPORATE SOURCE: Insert Therapeutics, Inc., Pasadena, CA, USA
SOURCE: Cancer Biology & Therapy (2004), 3(7), 641-650
CODEN: CBTAAO; ISSN: 1538-4047
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Short nucleic acid sequences specific to oncogene targets such as bcl-2, bcr-abl, and c-myc have been shown to exhibit specific anticancer activity in vitro through antigene or antisense activity. Efficient in vivo delivery of oligonucleotides remains a major limitation for the therapeutic application of these mols. We report herein on the preparation of transferrin-modified nanoparticles containing DNAzymes (short catalytic single-stranded DNA mols.) for tumor targeting as well as their biodistribution using various methods of administration in the mouse. Linear, β- **cyclodextrin**-based **polymers** are complexed with DNAzyme mols. to form sub-50 nm particles termed "polyplexes". The surface properties of the **cyclodextrin**-containing polyplexes are modified by exploiting the ability of the β-**cyclodextrin** substructure and adamantane to form inclusion complexes. Accordingly, conjugates of adamantane with poly(ethylene glycol) (PEG) are prepared and combined with the polyplexes. The adamantane form inclusion complexes with the surface **cyclodextrins** of the polyplexes to provide a sterically stabilizing layer of PEG. The stabilized polyplexes are also modified with transferrin for increasing targeting to tumor cells expressing transferrin receptors. The preparation, characterization, and in vitro application of these nanoparticles are discussed. The transferrin-polyplexes containing fluorescently-labeled DNAzyme mols. are administered to tumor-bearing nude mice and their biodistribution and clearance kinetics are monitored using a fluorescence imaging system. Four methods of administration are studied: i.p. bolus and infusion, i.v. bolus, and s.c. injection. DNAzymes packaged in polyplex formulations are concentrated and retained in tumor tissue and other organs, whereas unformulated DNAzyme is eliminated from the body within 24 h post-injection. I.v. and i.p. bolus injections result in the highest fluorescent signal (DNAzyme) at the tumor site. Tumor cell uptake is observed with i.v. bolus injection only, and intracellular delivery requires transferrin targeting.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1028233 CAPLUS
DOCUMENT NUMBER: 142:140892
TITLE: **Cyclodextrin**-based pharmaceutics: past, present and future
AUTHOR(S): **Davis, Mark E.**; Brewster, Marcus E.

CORPORATE SOURCE: Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Nature Reviews Drug Discovery (2004), 3(12), 1023-1035
CODEN: NRDDAG; ISSN: 1474-1776
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Cyclodextrins** are cyclic oligomers of glucose that can form water-soluble inclusion complexes with small mols. and portions of large compds. These biocompatible, cyclic oligosaccharides do not elicit immune responses and have low toxicities in animals and humans. **Cyclodextrins** are used in pharmaceutical applications for numerous purposes, including improving the bioavailability of drugs. Current **cyclodextrin**-based therapeutics are described and possible future applications discussed. **Cyclodextrin**-containing **polymers** are reviewed and their use in drug delivery presented. Of specific interest is the use of **cyclodextrin**-containing **polymers** to provide unique capabilities for the delivery of nucleic acids.

REFERENCE COUNT: 161 THERE ARE 161 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1017744 CAPLUS
DOCUMENT NUMBER: 142:451516
TITLE: **Cyclodextrin**-containing **polymers** for gene delivery
AUTHOR(S): Pun, Suzie Hwang; **Davis, Mark E.**
CORPORATE SOURCE: University of Washington, Seattle, WA, USA
SOURCE: Polymeric Gene Delivery (2005), 187-210, 1 plate.
Editor(s): Amiji, Mansoor M. CRC Press LLC: Boca Raton, Fla.
CODEN: 69GCXS; ISBN: 0-8493-1934-X
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review describes **cyclodextrin**-based **polymeric** gene delivery systems that self-assemble with nucleic acid to form small nanoparticles. The properties of the nanoparticles can be easily modified by the addition of adamantane-based conjugates that also self-assemble with the particles by inclusion complex formation. Thus, this type of gene delivery system is the first to be completely formed via self-assembly. This technol. provides for the potential of imparting the functional complexity that is vital to viral delivery efficiency and success with the simplicity of a synthetic, modular system.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:885945 CAPLUS
DOCUMENT NUMBER: 142:62492
TITLE: Synthetic Biocompatible **Cyclodextrin**-Based Constructs for Local Gene Delivery to Improve Cutaneous Wound Healing
AUTHOR(S): Bellocq, Nathalie C.; Kang, David W.; Wang, Xuehui; Jensen, Gregory S.; Pun, Suzie H.; Schluep, Thomas; Zepeda, Monica L.; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc., Pasadena, CA, 91107, USA
SOURCE: Bioconjugate Chemistry (2004), 15(6), 1201-1211
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The localized, sustained delivery of growth factors for wound healing therapy is actively being explored by gene transfer to the wound site. Biocompatible matrixes such as bovine collagen have demonstrated usefulness in sustaining gene therapy vectors that express growth factors in local sites for tissue repair. Here, new synthetic biocompatible materials are prepared and shown to deliver a protein to cultured cells via the use of an adenoviral delivery vector. The synthetic construct consists of a linear, β- **cyclodextrin**-containing **polymer** and an adamantane-based crosslinking **polymer**. When the two **polymers** are combined, they create an extended network by the formation of inclusion complexes between the **cyclodextrins** and adamantanes. The properties of the network are altered by controlling the **polymer** mol. wts. and the number of adamantanes on the crosslinking **polymer**, and these modifications and others such as replacement of

the β- **cyclodextrin** (host) and adamantane (guest) with other **cyclodextrins** (hosts such as α, γ, and substituted members) and inclusion complex forming mols. (guests) provide the ability to rationally design network characteristics. Fibroblasts exposed to these synthetic constructs show proliferation rates and migration patterns similar to those obtained with collagen. Gene delivery (green fluorescent protein) to fibroblasts via the inclusion of adenoviral vectors in the synthetic construct is equivalent to levels observed with collagen. These in vitro results suggest that the synthetic constructs are suitable for in vivo tissue repair applications.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:597673 CAPLUS
DOCUMENT NUMBER: 141:326368
TITLE: PEGylation significantly affects cellular uptake and intracellular trafficking of non-viral gene delivery particles
AUTHOR(S): Mishra, Swaroop; Webster, Paul; **Davis, Mark E.**
CORPORATE SOURCE: Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: European Journal of Cell Biology (2004), 83(3), 97-111
CODEN: EJCBDN; ISSN: 0171-9335
PUBLISHER: Elsevier GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vitro studies of non-viral gene delivery vectors are typically not performed at physiol. conditions, and thus may not provide meaningful results for in vivo investigations. We determine if polycation-plasmid DNA complexes (polyplexes) exploited for in vitro studies behave similarly to variants more applicable to in vivo use by examining their cellular uptake and trafficking. Branched polyethylenimine (25 kDa) or a linear β-**cyclodextrin**-containing **polymer** are each used to formulate polyplexes, which can be PEGylated (PEG: poly(ethylene glycol)) to create particles stable in physiol. salt concns. Particle size, cellular uptake, intracellular trafficking, and reporter gene expression are reported for polyplexes and for their PEGylated variants. PEGylation confers salt stability to particles but produced a reduction in luciferase expression. Examination of in vitro particle internalization by transmission electron microscopy shows unmodified polyplexes entering cells as large aggregates while PEGylated particles remain small and discrete, both outside and within cells. Unmodified and PEGylated particles enter cells through the endocytic pathway and accumulate in a perinuclear region. Immunolabeling reveals unpackaged exogenous DNA in the cytoplasm and nuclei. It appears all particle types traffic towards the nucleus within vesicles and undergo degradation in vesicles and/or cytoplasm, and eventually some exogenous DNA enters the nucleus, where it is transcribed. In comparing polyplexes and their PEGylated variants, significant differences in particle morphol., cellular uptake, and resultant expression suggest that in vitro studies should be conducted with particles prepared for physiol. conditions if the results are to be relevant to in vivo performance.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:520083 CAPLUS
DOCUMENT NUMBER: 141:212548
TITLE: **Cyclodextrin**-Modified Polyethylenimine **Polymers** for Gene Delivery
AUTHOR(S): Pun, Suzie H.; Bellocq, Nathalie C.; Liu, Aijie; Jensen, Greg; Machemer, Todd; Quijano, Erlinda; Schluep, Thomas; Wen, Shufen; Engler, Heidrun; Heidel, Jeremy; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics Inc., Pasadena, CA, 91107, USA
SOURCE: Bioconjugate Chemistry (2004), 15(4), 831-840
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Linear and branched poly(ethylenimines), lPEI and bPEI, resp., grafted with β- **cyclodextrin** are prepared to give CD-lPEI and CD-bPEI, resp., and are investigated as in vitro and in vivo nonviral gene delivery agents. The in vitro toxicity and transfection efficiency are sensitive to the level of **cyclodextrin** grafting. The **cyclodextrin** -containing polycations, when combined with adamantane-poly(ethylene glycol)

(AD-PEG) conjugates, form particles that are stable at physiol. salt concns. PEGylated CD-lPEI-based particles give in vitro gene expression equal to or greater than lPEI as measured by the percentage of EGFP expressing cells. Tail vein injections into mice of 120 μg of plasmid DNA formulated with CD-lPEI and AD-PEG do not reveal observable toxicities, and both nucleic acid accumulation and expression are observed in liver.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:331929 CAPLUS
DOCUMENT NUMBER: 140:363027
TITLE: **Cyclodextrin**-modified **polymer** carriers coupled to biorecognition molecules for drug delivery
INVENTOR(S): Bellocq, Nathalie C.; **Davis, Mark E.**; Pun, Suzie Hwang
PATENT ASSIGNEE(S): Insert Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004032862	A2	20040422	WO 2003-US31991	20031008
WO 2004032862	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2501132	AA	20040422	CA 2003-2501132	20031008
US 2004109888	A1	20040610	US 2003-681745	20031008
EP 1549269	A2	20050706	EP 2003-786526	20031008
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003015198	A	20050830	BR 2003-15198	20031008

PRIORITY APPLN. INFO.: US 2002-417373P P 20021009
WO 2003-US31991 W 20031008

AB The application discloses **cyclodextrin**-modified materials for carrying drugs and other active agents, such as nucleic acids. Compns. are also disclosed of **cyclodextrin**-modified materials that release such active agents under controlled conditions. The invention also discloses compns. of **cyclodextrin**-modified **polymer** carriers that are coupled to biorecognition mols. for assisting the delivery of drugs to their site of action. A number of examples are given for preparation of **cyclodextrin**-PEG derivative conjugates.

L7 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:272544 CAPLUS
DOCUMENT NUMBER: 141:64547
TITLE: Antitumor activity of β- **cyclodextrin** **polymer**-camptothecin conjugates
AUTHOR(S): **Cheng, Jianjun; Khin, Kay T.; Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc., Pasadena, CA, 91107, USA
SOURCE: Molecular Pharmaceutics (2004), 1(3), 183-193
CODEN: MPOHBP; ISSN: 1543-8384
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antitumor activity of linear, β- **cyclodextrin** **polymer** (CDP)-camptothecin (CPT) conjugates (HGGG6, LGGG10, HG6, and HGGG10) is investigated in nude mice bearing human LS174T colon carcinoma tumors. These conjugates differ in **polymer** mol. mass [97 kDa (H) or 35 kDa (L)], CDP-CPT linker structure [glycine (G) or triglycine (GGG)], and CPT loading [ca. 6 wt % (6) or 10 wt % (10)].

Maximum tolerable doses (MTDs) of the three conjugates, LGGG10, HG6, and HGGG10, are determined to be 36, 9, and 9 mg of CPT/kg, resp., while the MTD of the CDP alone exceeds 240 mg/kg (highest value investigated). The three CDP-CPT conjugates with high **polymer** mol. masses (HGGG6, HG6, and HGGG10) demonstrate antitumor activity at their MTDs superior to that of CPT at the same amount and to that of irinotecan at its optimal dose. They also show tumor growth inhibition that is superior to that of the conjugate containing the low-mol. mass **polymer** (LGGG10) at the same dose of CPT. No significant effects of CPT weight loading or linker structure on tumor growth delay are observed However, conjugates containing G appear to be less toxic than these with GGG. These antitumor studies demonstrate that the CDP-based conjugates of CPT exhibit tumor growth inhibition superior to that of CPT or irinotecan at the conditions employed in this study. The striking observation is that a short course of treatment with the **polymer** conjugates gives long-term control of tumor growth that does not occur with either CPT or irinotecan. Intracellular CDPs are demonstrated by analyzing cells that were cultured in the presence of rhodamine-labeled CDP (HRhod) containing medium using both confocal microscopy and flow cytometry. The long-term therapeutic efficacy of CDP-CPT conjugates observed in mice may in part be due to the sustained release of CPT from these conjugates in the acidic, intracellular compartments since these conjugates are shown to have significantly slower release rates at acidic pH than at physiol. pH.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:269859 CAPLUS
DOCUMENT NUMBER: 140:297547
TITLE: Methods and compositions for therapeutic use of RNA interference for attenuating expression of a target gene
INVENTOR(S): **Davis, Mark E.**; Jensen, Gregory S.; Pun, Suzie Hwang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Pat. Appl. 2003 157,030.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004063654	A1	20040401	US 2003-440506	20030515
US 2003157030	A1	20030821	US 2002-288230	20021104
CA 2465860	AA	20040422	CA 2002-2465860	20021104
AU 2002368202	A1	20040504	AU 2002-368202	20021104
JP 2005527639	T2	20050915	JP 2004-543172	20021104
EP 1575976	A2	20050921	EP 2002-807994	20021104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:

US 2001-336314P	P	20011102
US 2001-337304P	P	20011105
US 2002-418909P	P	20021015
US 2002-288230	A2	20021104
WO 2002-US35453	W	20021104

AB The invention provides methods and compns. for attenuating expression of a target gene in vivo. In general, the method includes administering RNAi constructs (e.g. small-interfering RNAs (i.e., siRNAs) that are targeted to particular mRNA sequences, or nucleic acid material that can produce siRNAs in a cell), in an amount sufficient to attenuate expression of a target gene by an RNA interference mechanism, e.g., in a sequence-dependent, PKR-independent manner. In particular, the method can be used to alter the growth, survival or differentiation of cells for therapeutic and cosmetic purposes.

L7 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:220231 CAPLUS
DOCUMENT NUMBER: 140:276173
TITLE: **Cyclodextrin**-based **polymers** for therapeutics delivery
INVENTOR(S): **Cheng, Jianjun; Davis, Mark E.; Khin, Kay T.**
PATENT ASSIGNEE(S): Insert Therapeutics, Inc., USA

SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022099	A2	20040318	WO 2003-US27588	20030904
WO 2004022099	A3	20041028		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2497792	AA	20040318	CA 2003-2497792	20030904
AU 2003278764	A1	20040329	AU 2003-278764	20030904
EP 1534340	A2	20050601	EP 2003-770286	20030904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003014042	A	20050705	BR 2003-14042	20030904
JP 2006502301	T2	20060119	JP 2004-569982	20030904
US 2004077595	A1	20040422	US 2003-656838	20030905

PRIORITY APPLN. INFO.:		
US 2002-408855P	P	20020906
US 2002-422830P	P	20021031
US 2003-451998P	P	20030304
WO 2003-US27588	W	20030904

AB The present invention relates to novel compns. of therapeutic **cyclodextrin**-containing **polymeric** compds. designed as a carrier for delivery of small mol. therapeutics and pharmaceutical compns. thereof. These **cyclodextrin**-containing **polymers** improve drug stability and solubility, and reduce toxicity of the small mol. therapeutics when used in vivo. Furthermore, by selecting from a variety of linker groups and targeting ligands the **polymers** present methods for controlled delivery of the therapeutic agents. The invention also relates to methods of treating subjects with the therapeutic compns. described herein. The invention further relates to methods for conducting pharmaceutical business comprising manufacturing, licensing, or distribution kits containing or relating to the **polymeric** compds. described herein.

L7 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:79958 CAPLUS
DOCUMENT NUMBER: 141:28449
TITLE: Antitumor activity of linear-**cyclodextrin** **polymer** conjugates of camptothecin
AUTHOR(S): **Cheng, Jianjun; Khin, Kay T.**; Liu, Aijie; Jensen, Greg; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc., Pasadena, CA, 91107, USA
SOURCE: AIChE Annual Meeting, Conference Proceedings, San Francisco, CA, United States, Nov. 16-21, 2003 (2003), 95-99. American Institute of Chemical Engineers: New York, N. Y.
CODEN: 69EZVH; ISBN: 0-8169-0941-5
DOCUMENT TYPE: Conference; (computer optical disk)
LANGUAGE: English

AB The synthesis of linear-**cyclodextrin** **polymers** that are conjugated with camptothecin (CPT) and their antitumor effects in nude mice bearing human LS174T colon carcinoma tumors are reported. Conjugates that differ in **polymer** mol. weight (97 kDa or 35 kDa; above and below the renal clearance limit, resp.), **polymer**-CPT linker structure (glycine or triglycine) and CPT loading (6% or 10%), are prepared and their behavior compared to CPT alone and the FDA approved prodrug of camptothecin - irinotecan - that is currently first line therapy for colorectal cancer. The **polymer** conjugates increase the solubility of CPT by over a factor of 4000 and the chemical used for the conjugation assures that the CPT on the **polymer** remains in the active form. Beginning with median tumor wts. of 100 mg, the end point was fixed at a median tumor weight of 1500 mg. Using DW5 as the control, the median time to end point (TTE) is 35 days. With CPT and irinotecan dosed at their maximum

tolerable dose (MTD, q4dX2 and qwkX3, resp.), the TTE's are 51 and 69 days, resp. With the **cyclodextrin polymer**-CPT conjugates dosed at their MTD (q4dX3), no TTE is reached (study ended at day 114). Thus, the **polymer** conjugates give long term control over tumor growth (study ended 105 days after the final dose was given to the mice - they were dosed on days 1, 4 and 9 of the 114 day study). Addnl., at a constant amount of CPT injected, the conjugates with higher mol. weight **polymers** are significantly more efficacious than the lower mol. weight analogs and this is likely due to increased accumulation in tumors.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:864083 CAPLUS
DOCUMENT NUMBER: 140:82077
TITLE: Transferrin-Containing, **Cyclodextrin Polymer**-Based Particles for Tumor-Targeted Gene Delivery
AUTHOR(S): Bellocq, Nathalie C.; Pun, Suzie H.; Jensen, Gregory S.; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics Inc., Pasadena, CA, USA
SOURCE: Bioconjugate Chemistry (2003), 14(6), 1122-1132
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transferrin is a well-studied ligand for tumor targeting due to upregulation of transferrin receptors in numerous cancer cell types. Here, we report the development of a transferrin-modified, **cyclodextrin polymer**-based gene delivery system. The delivery system is comprised of a nanoparticle (formed by condensation of a **cyclodextrin** polycation with nucleic acid) that is surface-modified to display poly(ethylene glycol) (PEG) for increasing stability in biol. fluids and transferrin for targeting of cancer cells that express transferrin receptor. A transferrin-PEG-adamantane conjugate is synthesized for nanoparticle modification. The transferrin conjugate retains high receptor binding and self-assembles with the nanoparticles by adamantane (host) and particle surface **cyclodextrin** (guest) inclusion complex formation. At low transferrin modification, the particles remain stable in physiol. salt concns. and transfect K562 leukemia cells with increased efficiency over untargeted particles. The increase in transfection is eliminated when transfections are conducted in the presence of excess free transferrin. The transferrin-modified nanoparticles are appropriate for use in the systemic delivery of nucleic acid therapeutics for metastatic cancer applications.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:696944 CAPLUS
DOCUMENT NUMBER: 139:219362
TITLE: Carbohydrate-modified **polymers**, compositions and uses related thereto
INVENTOR(S): Bellocq, Nathalie C.; **Cheng, Jianjun**; **Davis, Mark E.**; Pun, Suzie Hwang
PATENT ASSIGNEE(S): Insert Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072637	A1	20030904	WO 2003-US5688	20030224

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2476769	AA	20030904	CA 2003-2476769	20030224
AU 2003239121	A1	20030909	AU 2003-239121	20030224
US 2004087024	A1	20040506	US 2003-372723	20030224
EP 1476492	A1	20041117	EP 2003-733834	20030224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005518470	T2	20050623	JP 2003-571337	20030224
CN 1639228	A	20050713	CN 2003-804454	20030224

PRIORITY APPLN. INFO.: US 2002-358830P P 20020222
US 2002-417747P P 20021010
WO 2003-US5688 W 20030224

AB This application discloses compns. of carbohydrate-modified **polymers**, such as polyethylenimine modified with **cyclodextrin** moieties, for carrying drugs and other active agents, such as nucleic acids. Compns. are also disclosed of carbohydrate-modified **polymer** carriers that release such agents under controlled conditions. The invention also discloses compns. of carbohydrate-modified **polymer** carriers that are coupled to biorecognition mols. for targeting the delivery of drugs to their site of action.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:666514 CAPLUS
DOCUMENT NUMBER: 140:169415
TITLE: Linear, **cyclodextrin**-based **polymers** for the delivery of broad ranging therapeutics
AUTHOR(S): **Cheng, Jianjun**; Bellocq, Nathalie; Pun, Suzie Hwang; **Khin, Kay T.**; Liu, Aijie; Jensen, Gregory S.; Dartt, Christopher B.; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc., Pasadena, CA, 91107, USA
SOURCE: PMSE Preprints (2003), 89, 52
CODEN: PPMRA9; ISSN: 1550-6703
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (computer optical disk)
LANGUAGE: English
AB **Cyclodextrins** (CD) are cyclic oligomers of α-1,4-linked glucopyranose units and capable of forming inclusion complexes with small mols. and sidechains of larger compds. The guest-host properties of CDs have been extensively investigated, and their use as solubilizing agents for small mol. drugs exploited worldwide. Numerous types of **cyclodextrin**-containing **polymers** have been prepared In 1999, some of us reported the preparation of a completely new type of linear, β-CD-containing **polymer** and showed that this polycation was capable of delivering plasmid DNA into cultured cells. Since that time, the authors have extended the concept of linear, water-soluble CD-containing **polymers** to include species that are pos., neutral and neg. charged, and have used these materials to deliver therapeutics of all sizes ranging from small mols. (can be less than 1 nm in size), to oligonucleotides (1-10 nm) and full plasmids (30-200 nm when condensed). This presentation focuses on: (i) the synthetic strategy for the preparation of linear, water-soluble, CD-containing **polymers**, [ii] the different features that have successfully been designed into these materials, and (iii) the results obtained from animal models that demonstrate the successful delivery of all therapeutic size ranges.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:666072 CAPLUS
DOCUMENT NUMBER: 139:328131
TITLE: Synthesis of Linear, β- **Cyclodextrin** -Based **Polymers** and Their Camptothecin Conjugates
AUTHOR(S): **Cheng, Jianjun; Khin, Kay T.**; Jensen, Gregory S.; Liu, Aijie; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc., Pasadena, CA, 91107, USA
SOURCE: Bioconjugate Chemistry (2003), 14(5), 1007-1017
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 6A,6D-Bis-(2-amino-2-carboxylethylthio)-6A,6D-dideoxy-β-

cyclodextrin 1, a diamino acid derivative of β-**cyclodextrin**, is synthesized and condensed with difunctionalized PEG comonomers to give linear, high mol. weight (Mw over 50 kDa) β-**cyclodextrin**-based **polymers** (2-4) with pendant functionality (carboxylate). 2-4 Are all highly soluble in aqueous solns. (over 200 mg/mL). 20-O-trifluoroglycinylcamptothecin, 5a, and 20-O-trifluoroglycinylglycinylglycinylcamptothecin, 5b, are synthesized and conjugated to 2 to give **polymer**-camptothecin (CPT) prodrugs. The solubility of CPT is increased by more than three orders of magnitude when it is conjugated to 2. The rates of CPT release from the conjugates HGGG6 (high mol. weight **polymer** (Mw 97 kDa), glyglygly linker and 6 wt % CPT loading) and HG6 (high MW **polymer** (Mw 97 kDa), gly linker and 6 wt % CPT loading) in either mouse or human plasma are dramatically accelerated over the rates of pure hydrolysis at pH = 7.4, indicating the presence of enzymic cleavage as a rate-determining step at this pH in the release of the CPT. The pH of aqueous solution has a large effect on hydrolysis rate of CPT from HGGG6 and HG6; the lower the pH, the slower the rate in the range at 4.1 ≤ pH ≤ 13.1. The IC50's of **polymer** 2e, CPT, and the CPT conjugates HG6 and HGGG6 are found to be cell-line dependent with LS174T, HT29, A2780, and PC3 cells using in vitro MTT assays. The parent **polymer** 2e has very low toxicity to all cultured cells tested.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:656197 CAPLUS
DOCUMENT NUMBER: 139:202481
TITLE: Methods and compositions for therapeutic use of RNA interference
INVENTOR(S): **Davis, Mark E.**; Jensen, Gregory S.; Pun, Suzie Hwang
PATENT ASSIGNEE(S): Insert Therapeutics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 53 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003157030	A1	20030821	US 2002-288230		20021104
CA 2465860	AA	20040422	CA 2002-2465860		20021104
WO 2004033620	A2	20040422	WO 2002-US35453		20021104
WO 2004033620	A3	20050728			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2002368202	A1	20040504	AU 2002-368202		20021104
JP 2005527639	T2	20050915	JP 2004-543172		20021104
EP 1575976	A2	20050921	EP 2002-807994		20021104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR, BG, CZ, EE, SK					
US 2004063654	A1	20040401	US 2003-440506		20030515
PRIORITY APPLN. INFO.:			US 2001-336314P	P	20011102
			US 2001-337304P	P	20011105
			US 2002-418909P	P	20021015
			US 2002-288230	A2	20021104
			WO 2002-US35453	W	20021104

AB The present invention provides methods and compns. for attenuating expression of a target gene in vivo. In general, the method includes administering RNAi constructs (such as small-interfering RNAs (i.e., siRNAs) that are targeted to particular mRNA sequences, or nucleic acid material that can produce siRNAs in a cell), in an amount sufficient to attenuate expression of a target gene by an RNA interference mechanism, e.g., in a sequence-dependent, PKR-independent manner. In particular, the subject method can be used to alter the growth, survival or differentiation of cells for therapeutic and cosmetic purposes.

L7 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:636419 CAPLUS
TITLE: Linear, **cyclodextrin**-based **polymers** for the delivery of broad ranging therapeutics
AUTHOR(S): **Cheng, Jianjun**; Bellocq, Nathalie; Pun, Suzie Hwang; **Khin, Kay T.**; Jensen, Gregory S.; Liu, Aijie; Dartt, Christopher B.; **Davis, Mark E.**
CORPORATE SOURCE: Insert Therapeutics, Inc, Pasadena, CA, 91107, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), PMSE-034. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Linear, water-soluble, **cyclodextrin**-containing **polymers** are a new class of biocompatible materials that can be designed to provide desired properties and characteristics that are not achievable with other **polymer** delivery systems. A generalized synthetic strategy for these materials, a brief overview of their properties and results in animal models supporting their use as delivery vehicles for small mol. drugs, plasmid DNA, and oligonucleotides will be presented.

L7 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:494960 CAPLUS
DOCUMENT NUMBER: 140:31228
TITLE: **Cyclodextrin**-containing **polymers** for gene delivery
AUTHOR(S): **Davis, Mark E.**; Bellocq, Nathalie C.
CORPORATE SOURCE: Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Journal of Inclusion Phenomena and Macrocyclic Chemistry (2002), Volume Date 2003, 44(1-4), 17-22
CODEN: JIPCF5; ISSN: 1388-3127
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion of results. **Cyclodextrin**-containing **polymers** are now being explored as vehicles for delivering nucleic acids into cells. The structures of the **cyclodextrin**-containing polycations affect the nucleic acid delivery efficiencies and their toxicities. Of interest is the fact that the **cyclodextrin** -containing **polymers** reveal lower toxicities than **polymers** that lack the **cyclodextrins**. The **cyclodextrins** endow the nucleic acid delivery vehicles with the ability to be modified by compds. that form inclusion complexes with the **cyclodextrins**, and these modifications can be performed without disruption of the **polymer**-nucleic acid interactions. Thus, **cyclodextrin** -containing **polymers** provide unique properties for gene delivery.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:381559 CAPLUS
DOCUMENT NUMBER: 138:358341
TITLE: Optimization of **cyclodextrin**-containing **polymers** specifically designed for gene delivery
AUTHOR(S): Bellocq, Nathalie C.; Hwang, Sue J.; **Davis, Mark E.**
CORPORATE SOURCE: Dep. of Chem. Eng., California Inst. of Technol., Pasadena, CA, 91125, USA
SOURCE: Polymeric Materials Science and Engineering (2001), 84, 809-810
CODEN: PMSEDG; ISSN: 0743-0515
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cationic **polymers** synthesized by copolymg. **cyclodextrin** -dicysteamine with a difunctionalized comonomer are able to self-assemble with DNA and transfect cultured cells. The structure of β-**cyclodextrin polymers** dets. performance in DNA delivery cell toxicity. The low toxicity of theses **polymers** make them attractive agents for gene delivery applications.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:227005 CAPLUS
DOCUMENT NUMBER: 138:358338
TITLE: Structural effects of carbohydrate-containing polycations on gene delivery. 3. **cyclodextrin** type and functionalization
AUTHOR(S): Popielarski, Stephen R.; Mishra, Swaroop; **Davis, Mark E.**
CORPORATE SOURCE: Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Bioconjugate Chemistry (2003), 14(3), 672-678
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Linear cationic β- **cyclodextrin** (β-CD)-based **polymers** can form polyplexes with plasmid DNA and transfect cultured cells. The effectiveness of the gene delivery and the cellular toxicity has been related to structural features in these polycations. Previous β-CD polycations were prepared from the cocondensation of 6A,6D-dideoxy-6A,6D-diamino-β-CD monomers with other difunctionalized monomers such as di-Me suberimidate (DMS). Here, the type of CD and its functionalization are varied by synthesizing numerous 3A,3B-dideoxy-3A,3B-diamino-β- and γ-CD monomers. Both alkyl- and alkoxydiamines are prepared in order to vary the nature of the spacing between the CD and the primary amines in the monomers. These diamino-CD-monomers are **polymd.** with DMS to yield amidine-based polycations. The nature of the spacer between the CD-ring and the primary amines of each monomer is found to influence both mol. weight and polydispersity of the polycations. When these polycations are used to form polyplexes with plasmid DNA, longer alkyl regions between the CD and the charge centers in the polycation backbone increase transfection efficiency and toxicity in BHK-21 cells, while increasing hydrophilicity of the spacer (alkoxy vs. alkyl) provides for lower toxicity. Further, γ-CD-based polycations are shown to be less toxic than otherwise identical β-CD-based polycations.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:222644 CAPLUS
DOCUMENT NUMBER: 139:281039
TITLE: Structure-property investigation of trehalose and β- **cyclodextrin**-based polycations for gene delivery
AUTHOR(S): Reineke, Theresa M.; **Davis, Mark E.**
CORPORATE SOURCE: Department of Chemistry, University of Cincinnati, Cincinnati, OH, 45255, USA
SOURCE: PMSE Preprints (2003), 88, 224-225
CODEN: PPMRA9; ISSN: 1550-6703
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (computer optical disk)
LANGUAGE: English
AB A series of **polymers** that contain a hexamethylene group, trehalose, and β- **cyclodextrin** were prepared to study the effects of polycation structure on gene delivery and toxicity. The charge center does not affect toxicity but does play a role in the delivery efficiency since the amidine polycations revealed higher gene expression levels than their quaternary ammonium derivs. Also, as the charge center was moved further away from the trehalose group, toxicity increased. The effect was not seen in the β- **cyclodextrin** polycations which indicates that by increasing the size of the carbohydrate group, toxicity can be reduced.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:185936 CAPLUS
TITLE: Structure-property investigation of trehalose and β- **cyclodextrin**-based polycations for gene delivery
AUTHOR(S): Reineke, Theresa M.; **Davis, Mark E.**
CORPORATE SOURCE: Department of Chemistry, University of Cincinnati,

Cincinnati, OH, 45221, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), PMSE-138. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Polycations have the ability to bind plasmid DNA (pDNA) through electrostatic interactions and condense it into particles that can be readily uptaken by cultured cells. Recent polycation structure-gene delivery studies have revealed that small changes in the mol. structure of **polymeric** vectors have substantial influences on DNA-binding and condensation, and on toxicity and gene delivery efficiency in vitro. The effects that structure has on toxicity and gene delivery efficiency are investigated here through synthesizing a series of amidine-based polycations that contain the carbohydrates trehalose and beta-**cyclodextrin** (CD) within the **polymer** backbone. The carbohydrate size (trehalose vs CD) and its distance from the DNA-binding charge centers affected the gene delivery behavior in BHK-21 cells. It was found that as the charge center was further removed from the carbohydrate unit, the toxicity increased. Also, as the size of the carbohydrate moiety increased from trehalose to CD, the toxicity was reduced. The absence of a carbohydrate in the polycation backbone produced high toxicity in vitro. All carbohydrate amidine polycations transfected BHK-21 cells to approx. the same level of gene expression up to a charge ratio of 20 +/-. In addition, the effects that polycation charge center type had on toxicity and gene delivery efficiency was investigated. A series of quaternary ammonium polycations analogous to the amidine systems (containing N,N,N',N'-tetramethyl-1,6-hexanediamine, trehalose, and CD) were synthesized and studied for in vitro gene delivery and toxicity. In all cases, it was found that the quaternary ammonium analogs exhibited similar toxicity profiles but lower gene expression values to their amidine analogs with BHK-21 cells. Also, transfection expts. conducted in the presence of chloroquine revealed increased gene expression from the quaternary ammonium containing polycations but not from the amidine systems. This result indicated that the amidine polycations have improved endosomal escape properties relative to the quaternary ammonium **polymers**.

L7 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:965257 CAPLUS
DOCUMENT NUMBER: 138:175678
TITLE: Structural Effects of Carbohydrate-Containing Polycations on Gene Delivery. 1. Carbohydrate Size and Its Distance from Charge Centers
AUTHOR(S): Reineke, Theresa M.; **Davis, Mark E.**
CORPORATE SOURCE: Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Bioconjugate Chemistry (2003), 14(1), 247-254
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cationic **polymers** have the ability to bind plasmid DNA (pDNA) through electrostatic interactions and condense it into particles that can be readily endocytosed by cultured cells. The effects that polycation structure has on toxicity and gene delivery efficiency are investigated here by synthesizing a series of amidine-based polycations that contain the carbohydrates D-trehalose and β- **cyclodextrin** (CD) within the polycation backbone. The carbohydrate size (trehalose vs CD) and its distance from the charge centers affect the gene delivery behavior in BHK-21 cells. It is found that as the charge center is further removed from the carbohydrate unit, the toxicity is increased. Also, as the size of the carbohydrate moiety is enlarged from trehalose to β-**cyclodextrin**, the toxicity is reduced. The absence of a carbohydrate in the polycation produces high toxicity. All carbohydrate polycations transfect BHK-21 cells to approx. the same level of gene expression.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:487421 CAPLUS
DOCUMENT NUMBER: 137:47645
TITLE: Preparation of adamantyl-polyethylene glycol

containing sugar and peptide residues and inclusion complexes as therapeutic agents

INVENTOR(S): Hwang, Pun Suzie; Gonzalez, Hector; **Davis, Mark E.**; Bellocq, Nathalie; **Cheng, Jianjun**

PATENT ASSIGNEE(S): California Institute of Technology, USA; Insert Therapeutics, Inc.

SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002049676	A2	20020627	WO 2001-US48620	20011219
WO 2002049676	A3	20021227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2431207	AA	20020627	CA 2001-2431207	20011219
AU 2002029065	A5	20020701	AU 2002-29065	20011219
US 2003008818	A1	20030109	US 2001-21312	20011219
US 7018609	B2	20060328		
US 2003017972	A1	20030123	US 2001-21294	20011219
EP 1351710	A2	20031015	EP 2001-990201	20011219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1491117	A	20040421	CN 2001-822729	20011219
BR 2001016346	A	20040706	BR 2001-16346	20011219
JP 2004523502	T2	20040805	JP 2002-551013	20011219
ZA 2003004562	A	20040803	ZA 2003-4562	20030611

PRIORITY APPLN. INFO.:		
US 2000-256341P	P	20001219
US 2000-256344P	P	20001219
US 2001-293543P	P	20010529
WO 2001-US48620	W	20011219

AB The invention provides a composition containing particulate composite of a **polymer** with a formula of adamantyl-(CH2)n-Ja-PEGx-Lb-(functional group)y wherein J is NH, C(O)NH(CH2)d, NHC(O)(CH2)d, XH2SS, CO2,(CH2)eOP(O)[O(CH2)e-adamantyl]O, peptide, polypeptide, NH(CO)CHR1NH(CO)CHR1NH; R1 is (CH2)aCO2H, (CH2)aCONH2; PEG is O(CH2CH2O)z; where z is 2-500; L is H, NH2, NH(CO)(CH2)e(CO)CH2, SO2CH:CH2, SS, CO2, carbohydrate residue; a is 0-1, b is 0-1; d is 0-6; e is 1-6; yr is 0-1, x is 0-1, and a therapeutic agent. The composition also contains a complexing agent. The **polymer** interacts with the complexing agent in a host-guest or a guest-host interaction to form an inclusion complex. A therapeutic composition of the invention may be used to deliver the therapeutic agent and to treat various disorders. Both the **polymer** of the particulate composite and the complexing agent may be used to introduce functionality into the therapeutic composition The invention also relates to a method of preparing a composition The method combines a therapeutic agent, a **polymer** having host or guest functionality, and a complexing agent having guest or host functionality to form the therapeutic composition The complexing agent forms an inclusion complex with the **polymer**. The invention also relates to a method of delivering a therapeutic agent. According to the method, a therapeutically effective amount of a therapeutic composition of the invention is administered to a mammal (e.g. human or animal) in recognized need of the therapeutic.

L7 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:294332 CAPLUS

DOCUMENT NUMBER: 137:52241

TITLE: Development of a Nonviral Gene Delivery Vehicle for Systemic Application

AUTHOR(S): Pun, Suzie Hwang; **Davis, Mark E.**

CORPORATE SOURCE: Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA

SOURCE: Bioconjugate Chemistry (2002), 13(3), 630-639
CODEN: BCCHES; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polycation vehicles used for in vitro gene delivery require alteration for successful application in vivo. Modification of polycations by direct grafting of addnl. components, e.g., PEG, either before or after DNA complexation, tend to interfere with **polymer**/DNA binding interactions; this is a particular problem for short polycations such as linear, β- **cyclodextrin**-containing polycations (βCDPs). Here, a new method of βCDP polyplex (polycation/DNA composite structures) modification is presented that exploits the ability to form inclusion complexes between **cyclodextrins** and adamantane. Surface-PEGylated βCDP polyplexes are formed by self-assembly of the polyplexes with adamantane-PEG conjugates. While unmodified polyplexes rapidly aggregate and precipitate in salt solns., the PEGylated βCDP polyplexes are stable at conditions of physiol. salt concentration Addition of targeting ligands to the adamantane-PEG conjugates allows for receptor-mediated delivery; galactosylated βCDP-based particles reveal selective targeting to hepatocytes via the asialoglycoprotein receptor. Galactosylated particles transfect hepatoma cells with 10-fold higher efficiency than glucosylated particles (control), but show no preferential transfection in a cell line lacking the asialoglycoprotein receptor. Thus, surface modification of βCDP-based polyplexes through the use of **cyclodextrin**/adamantane host/guest interactions endows the particles with properties appropriate for systemic application.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:204150 CAPLUS
TITLE: Optimization of **cyclodextrin-polymers** specifically designed for gene delivery
AUTHOR(S): Bellocq, Nathalie C.; Hwang, Sue J.; **Davis, Mark E.**
CORPORATE SOURCE: Department of Chemical Engineering, CALTECH, Pasadena, CA, 91125, USA
SOURCE: Abstracts of Papers, 221st ACS National Meeting, San Diego, CA, United States, April 1-5, 2001 (2001) PMSE-446
CODEN: 69FZD4
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Meeting Abstract
LANGUAGE: English
AB The current challenge in gene therapy is to develop a delivery method for transferring genetic material to desired cells in an effective, specific and non-toxic manner. Cationic **polymers** show promise for in vitro and in vivo delivery of DNA. Recently, we reported that linear, cationic β- **cyclodextrin** containing **polymers** (βCDPs) are capable of delivering plasmid DNA to mammalian cells with low toxicity. βCDPs were prepared by the **polymn.** of a difunctionalized β- **cyclodextrin** comonomer A with a difunctionalized comonomer B to give an (AB)X product with X between 4 and 6. TheβCDPs have the following structure: Different βCDPs were prepared by varying the structure of both comonomers A and B. We will show that the length of the "spacer group" Y (Y=0, 1) between the cup of the **cyclodextrin** and the cationic charge plays an important role in DNA binding. We will also show that some variations in the comonomer B, such as the number of methylene units (Z=-(CH2)n- with n=0,1, 2, 3, 4, 6), the use of biodegradable linkers (Z=-S-S-) or the use of pH sensitive linkers (Z=-NH-) have significant effects on in vitro transfection efficiencies and toxicities.

L7 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:115591 CAPLUS
DOCUMENT NUMBER: 134:300714
TITLE: Effects of Structure of β- **Cyclodextrin** -Containing **Polymers** on Gene Delivery
AUTHOR(S): Hwang, Suzie J.; Bellocq, Nathalie C.; **Davis, Mark E.**
CORPORATE SOURCE: Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Bioconjugate Chemistry (2001), 12(2), 280-290
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Linear cationic β- **cyclodextrin**-based **polymers** (βCDPs) are capable of forming polyplexes with nucleic acids and transfecting cultured cells. The βCDPs are synthesized by the condensation of a diamino-**cyclodextrin** monomer A with a diimidate comonomer B. In this paper, the effects of **polymer** structure on polyplex formation, in vitro transfection efficiency and toxicity are elucidated. By comparison of the βCDPs to polyamidines lacking **cyclodextrins**, the inclusion of a **cyclodextrin** moiety in the comonomer A units reduces the IC50s of the **polymer** by up to 3 orders of magnitude. The spacing between the cationic amidine groups is also important. Different **polymers** with 4, 5, 6, 7, 8, and 10 methylene units (βCDP4, 5, 6, 7, 8, and 10) in the comonomer B mol. are synthesized. Transfection efficiency is dependent on comonomer B length with up to 20-fold difference between **polymers** . Optimum transfection is achieved with the βCDP6 **polymer**. In vitro toxicity varied by 1 order of magnitude and the lowest toxicity is observed with βCDP8. The LD40 of the βCDP6 to mice is 200 mg/kg, making this **polymer** a promising agent for in vivo gene delivery applications.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:401687 CAPLUS
DOCUMENT NUMBER: 133:48948
TITLE: Supramolecular complexes containing therapeutic agents
INVENTOR(S): **Davis, Mark E.**; Gonzalez, Hector; Hwang, Suzie
PATENT ASSIGNEE(S): California Institute of Technology, USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000033885	A1	20000615	WO 1999-US28547		19991203
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2353552	AA	20000615	CA 1999-2353552		19991203
EP 1133318	A1	20010919	EP 1999-965967		19991203
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002531530	T2	20020924	JP 2000-586375		19991203
PRIORITY APPLN. INFO.:			US 1998-110847P	P	19981204
			US 1999-127856P	P	19990405
			WO 1999-US28547	W	19991203

AB A method of preparing a supramol. complex containing at least one therapeutic agent and a multi-dimensional **polymer** network is described. A supramol. complex prepared by a method of the invention is described. A method of treatment by administering a therapeutically effective amount of a supramol. complex of the invention is also described. Such a supramol. complex may be used as a delivery vehicle for various therapeutic agents. The **polymers** include linear or branched polyethyleneimine and **cyclodextrin** derivs.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:327605 CAPLUS
TITLE: Preparation and application of β-**cyclodextrin**-based **polymers** for gene delivery.
AUTHOR(S): Hwang, Sue Jean; Gonzalez, Hector; Bellocq, Nathalie; **Davis, Mark E.**

CORPORATE SOURCE: Department of Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), BIOT-376. American Chemical Society: Washington, D. C.
CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Various cationic **polymers**, such as polylysine and polyethylenimine, have been used as gene delivery vectors, but with limited application due to their toxicity. **Cyclodextrin** (CD) mols. have relatively low toxicity and were used to prepare linear, cationic **β- cyclodextrin polymers** by copolymg. difunctionalized β-CD monomers with various difunctionalized comonomers. These **polymers** were shown to transfect cultured cells with up to 75% efficiency and with low toxicity. The issues considered in designing the **polymers**, including the various difunctionzlied β-CD monomers and comonomers used, will be discussed.

L7 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:34909 CAPLUS
DOCUMENT NUMBER: 132:94914
TITLE: Preparation of linear **cyclodextrin** copolymers
INVENTOR(S): Gonzalez, Hector; Hwang, Suzie Sue Jean; **Davis, Mark E.**
PATENT ASSIGNEE(S): California Institute of Technology, USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001734	A1	20000113	WO 1999-US14298	19990625
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6509323	B1	20030121	US 1998-203556	19981202
CA 2336390	AA	20000113	CA 1999-2336390	19990625
AU 9948305	A1	20000124	AU 1999-48305	19990625
AU 763114	B2	20030710		
EP 1093469	A1	20010425	EP 1999-931889	19990625
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9911754	A	20011106	BR 1999-11754	19990625
JP 2002519482	T2	20020702	JP 2000-558134	19990625
RU 2243236	C2	20041227	RU 2001-102789	19990625
US 2002151523	A1	20021017	US 2002-97326	20020315
US 6884789	B2	20050426		

PRIORITY APPLN. INFO.:

US 1998-91550P	P	19980701
US 1998-203556	A	19981202
US 1999-339818	A3	19990625
WO 1999-US14298	W	19990625

AB Linear **cyclodextrin** copolymers containing an unoxidized and/or an oxidized **cyclodextrin** moiety integrated into the **polymer** backbone, useful as drug delivery vehicles, were prepared For example, substitution reaction of 6A,6D-diiodo-6A,6D-deoxy-β-**cyclodextrin** (2-step preparation by a known procedure given) with NaSCH2CH2NH2 gave 79% 6A,6D-bis(2-aminoethylthio)-6A6D-deoxy-β-**cyclodextrin**. This was stirred for 18 h at 80° in DMF under N with an equiv of MeOC(:NH)(CH2)6C(:NH)OMe-2HCl in the presence of Et3N to give 18% of a title copolymer (CD copolymer). Media containing doxorubicin and CD copolymer-doxorubicin complex (general complexation procedure given) were applied to cultured cell lines to show no toxicity to KB or KB-VI cell lines in the absence of doxorubicin.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:683617 CAPLUS
DOCUMENT NUMBER: 125:328078
TITLE: Enantioselective hydrogenation of prochiral C=C bonds over noble metal catalysts supported by β-**cyclodextrin polymer**
AUTHOR(S): Smith, Gerard V.; **Cheng**, **Jianjun**; Song, Ruozhi
CORPORATE SOURCE: Dep. of Chemistry and Biochemistry, Southern Illinois Univ., Carbondale, IL, 62901, USA
SOURCE: Chemical Industries (Dekker) (1996), 68(Catalysis of Organic Reactions), 479-483
CODEN: CHEIDI; ISSN: 0737-8025
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Platinum, palladium, rhodium, and ruthenium were deposited onto a β-**cyclodextrin**/epichlorohydrin copolymer (β-CDP) to produce enantioselective heterogeneous catalysts. These catalysts were prepared by refluxing a suspension of the corresponding metal salt and β-**cyclodextrin polymer** in either mixed methanol-water or methanol-NaOH. The ability of these catalysts to catalyze the enantioselective hydrogenation of carbon-carbon double bonds was tested with di-Me itaconate (DMI) and trans-2-methyl-2-pentenoic acid (TMPA).

L7 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:26773 CAPLUS
DOCUMENT NUMBER: 124:177025
TITLE: Platinum-group metal **cyclodextrin** complexes and their use as command-cure catalysts in silicones
AUTHOR(S): Lewis, Larry N.; Sumpter, Chris A.; **Davis**, **Mark**
CORPORATE SOURCE: Polymer and Inorganic Systems Laboratory, GE Research & Development, Schenectady, NY, 12301, USA
SOURCE: Journal of Inorganic and Organometallic Polymers (1995), 5(4), 377-90
CODEN: JIOPE4; ISSN: 1053-0495
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The command-cure concept is defined for a curable formulation as one with long work-life at ambient temperature and rapid cure time at elevated temperature This concept is explored for a curable silicone system, cured via hydrosilylation. CODMCl2 complexes (COD = 1,5-cyclo-octadiene; M = Pt, Pd) are reacted with beta-**cyclodextrin** (β-CD) to make 1:1 inclusion compds. (2 is the PD-containing compound and 4 is the Pt-containing compound). Compds. 2 and 4 were analyzed by 1H NMR and x-ray powder diffraction. Their catalytic ability was evaluated in a model system as well as a **polymeric** system that gels upon cure. Surprisingly, the Pd analog 2 was a good command-cure catalyst whereas the guest compound CODPdCl2 was not active in the hydrosilylation reaction. The Pt analog, 4, was an effective command-cure catalyst while the corresponding guest, CODPtCl2 was too active at low temperature in the hydrosilylation reaction. Addnl. Pt compds. and one Rh inclusion compound were evaluated as command cure catalysts. These inclusion compds. were: 1:1 β-CD:[CODRhCl]2, 1:1 β-CD:CpPtMe3, (Cp = cyclopentadienyl); 1:2 β-CD:MeCpPtMe3, 1:2 β-CD:CODPtMe2. The effectiveness of all these inclusion compds. were evaluated in a number of silicone systems.

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	18241	cyclodextrin	US-PGPUB; USPAT	OR	ON	2006/04/20 10:38
L2	809717	polymer$4	US-PGPUB; USPAT	OR	ON	2006/04/20 10:38
L3	4393	1 same 2	US-PGPUB; USPAT	OR	ON	2006/04/20 10:38
L4	184842	conjugat$4 bioconjugate (covalent$4 near4 attach$4)	US-PGPUB; USPAT	OR	ON	2006/04/20 10:39
L5	292	3 same 4	US-PGPUB; USPAT	OR	ON	2006/04/20 10:39
L6	292	5 and 1 and 2 and 4	US-PGPUB; USPAT	OR	ON	2006/04/20 10:39
L7	1124613	drug deliver$4 pharmaceutical$4 biodegrad$6 bioerod$6 hydrolyz$6 biohydrolyz$6 therapeutic	US-PGPUB; USPAT	OR	ON	2006/04/20 10:41
L8	278	6 and 7	US-PGPUB; USPAT	OR	ON	2006/04/20 10:41
L9	292	6 8	US-PGPUB; USPAT	OR	ON	2006/04/20 11:23
L10	710	1 same 4	US-PGPUB; USPAT	OR	ON	2006/04/20 11:23
L11	418	10 not 5	US-PGPUB; USPAT	OR	ON	2006/04/20 11:23
L12	393424	drug therapeutic receptor ligand	US-PGPUB; USPAT	OR	ON	2006/04/20 11:24
L13	322	10 same 12	US-PGPUB; USPAT	OR	ON	2006/04/20 11:24
L14	126	13 not 5	US-PGPUB; USPAT	OR	ON	2006/04/20 11:24

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	8954	cyclodextrin	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:33
L2	1459263	polymer$4 conjugat$4 bioconjugate	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:33
L3	1608	1 and 2	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:33
L4	1419381	polymer$4	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:33
L5	1552	1 and 4	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:33
L6	67631	conjugat$4 bioconjugate	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:34
L7	88	1 and 6	EPO; JPO; DERWENT	OR	ON	2006/04/20 11:34